MEMBRANOPROLIFERATVE GN

BY

AMIR M. ELOKELY
MRCP,MD

Is Membranoproliferative glomerulonephritis

A DISEASE

or

A HISTOLOGICAL DEFINITION?

MPGN

NOMENCLATURE

Other names

Mesangiocapillary, *Churg et al, 1970*

Hypocomplementic , persistent or chronic GN

Lobular GN

EPIDEMIOLOGY

- **MPGN presenting in childhood (primarily between the ages of 8 and 14 years) includes types I and III MPGN and DDD and is frequently idiopathic or associated with nephritic factors.**
- **MPGN presenting in adults (typically older than 18 years) is usually type I or type III and is commonly associated with cryoglobulinemia and HCV infection**

EPIDEMIOLOGY

- **In North America and Europe, MPGN (types I and III) and DDD constitute less than 5% of all primary glomerulonephritis.**

- **It occurs equally in males and females and in the United States is relatively more common in Caucasians than in African Americans.**

EPIDEMIOLOGY

- **The prevalence of MPGN type I is decreasing in Europe, presumably because some chronic infections are becoming less common.**
- **On the contrary, in the Middle East (Saudi Arabia), South America (Peru), and Africa (Nigeria), MPGN type I is still quite common because of its association with chronic bacterial, viral, and parasitic infections.**
- **DDD accounts for less than 20% of cases of MPGN in children and a very low percentage of cases in adults.**

MPGN

CLINICALLY

Variable Clinical Presentation

Differences in the pathogenesis of the disorder

Differences in the timing of the diagnostic biopsy relative to the clinical course

- Proteinuria
- Nephrotic Syndrome
- Nephritic Syndrome
- Hematuria
- Decreased C3 level
- Increased ASO titer
- RPGN
- CKD

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

Membranoproliferative Glomerulonephritis — A New Look at an Old Entity

Sanjeev Sethi, M.D., Ph.D., and Fernando C. Fervenza, M.D., Ph.D.

Sanjeev Sethi et al. N Engl J Med 2012;366:1119-31.

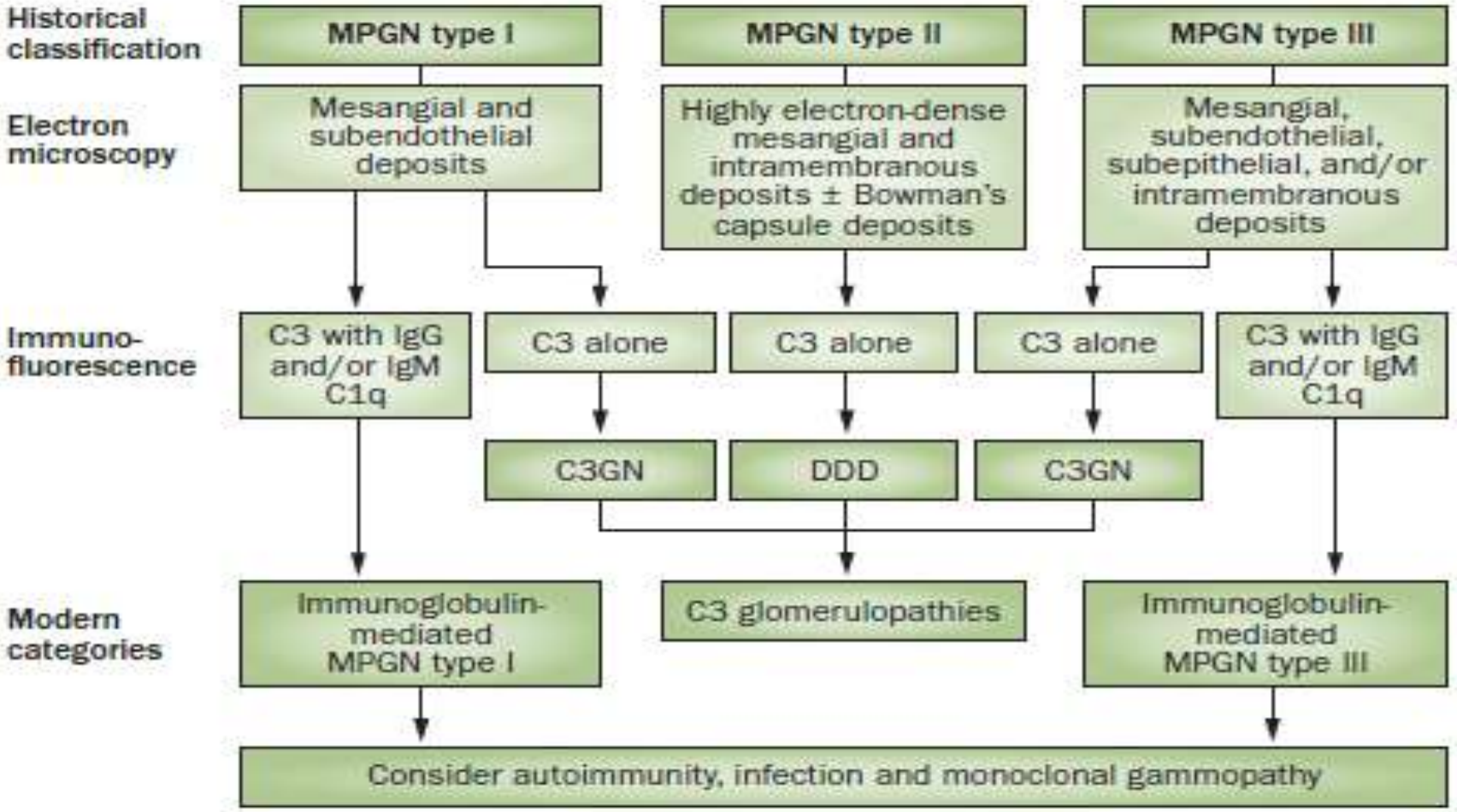
CJASN ePress. Published on January 9, 2014 as doi: 10.2215/CJN.06410613

Moving Points in Nephrology

Update on Membranoproliferative GN

Naveed Masani,* Kenar D. Jhaveri,† and Steven Fishbane†

CLASSIFICATION OF MPGN



CLASSIFICATION OF MPGN

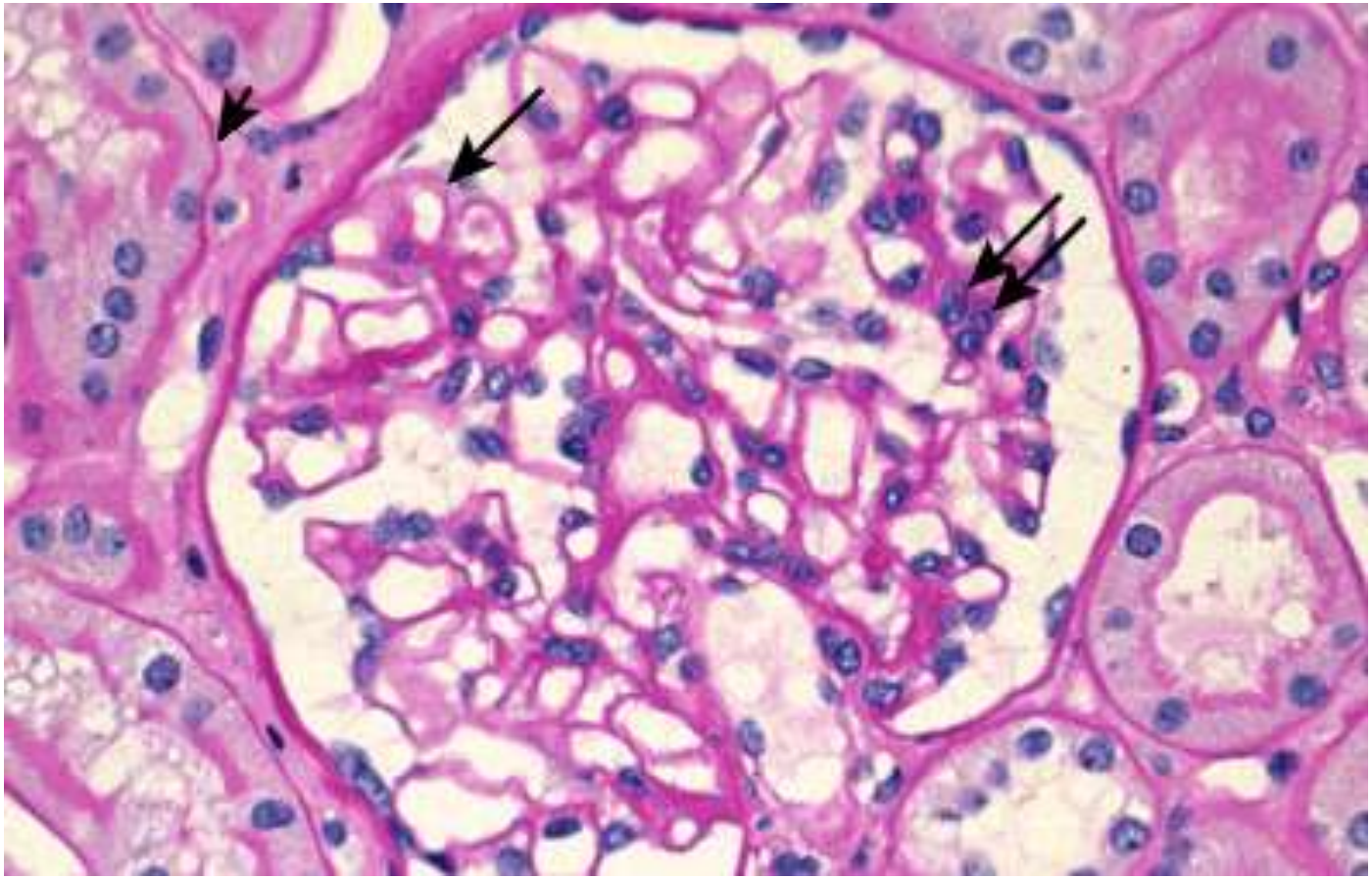
	Based on Electron Microscopy (Older)	Based on Immunofluorescence (Newer)
Classification	MPGN 1: Subendothelial MPGN	Immune complex–mediated MPGN Igs and complements on IF (paraproteins, viruses, autoimmune)
	MPGN 2: Dense subendothelial deposits (dense deposit disease)	Complement-mediated MPGN C3 dominant IF (C3 glomerulopathy)
	MPGN 3: Subendothelial membranoproliferative with intramembranous and subepithelial deposits	MPGN not related to complement or immune complex
		Negative IF (thrombotic microangiopathy)

IMMUNE COMPLEX CONDITION ASSOCIATED WITH MPGN PATTERN OF INJURY

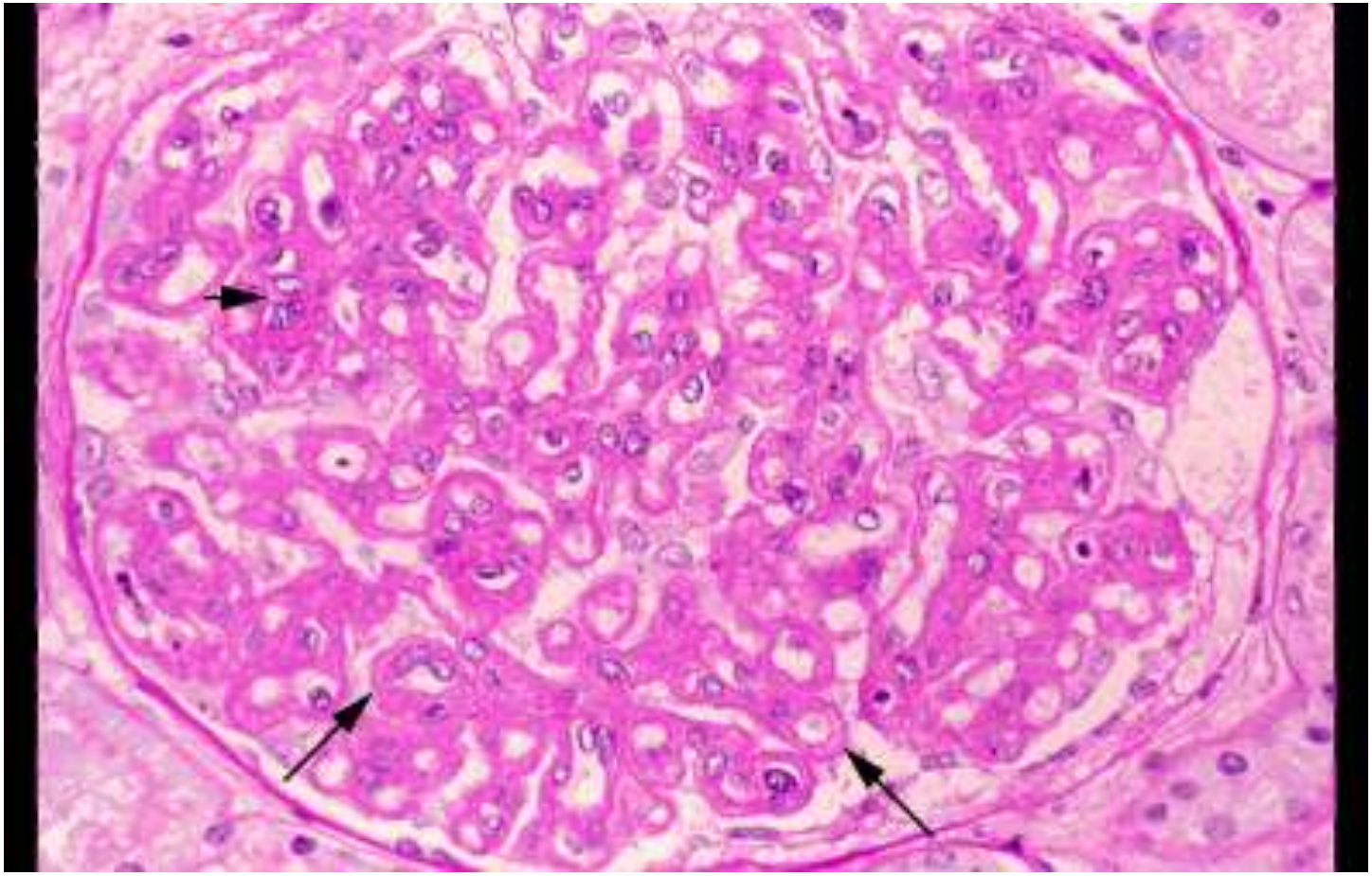
Autoimmune diseases
- Systemic lupus
- Sjogren's syndrome
- Rheumatoid arthritis
- Mixed connective tissue disease

Infections
- Hepatitis B
- Hepatitis C
- Endocarditis
- Shunt infections
- Visceral abscesses
- Leprosy
- Malaria
- Schistosomiasis
- Mycoplasma

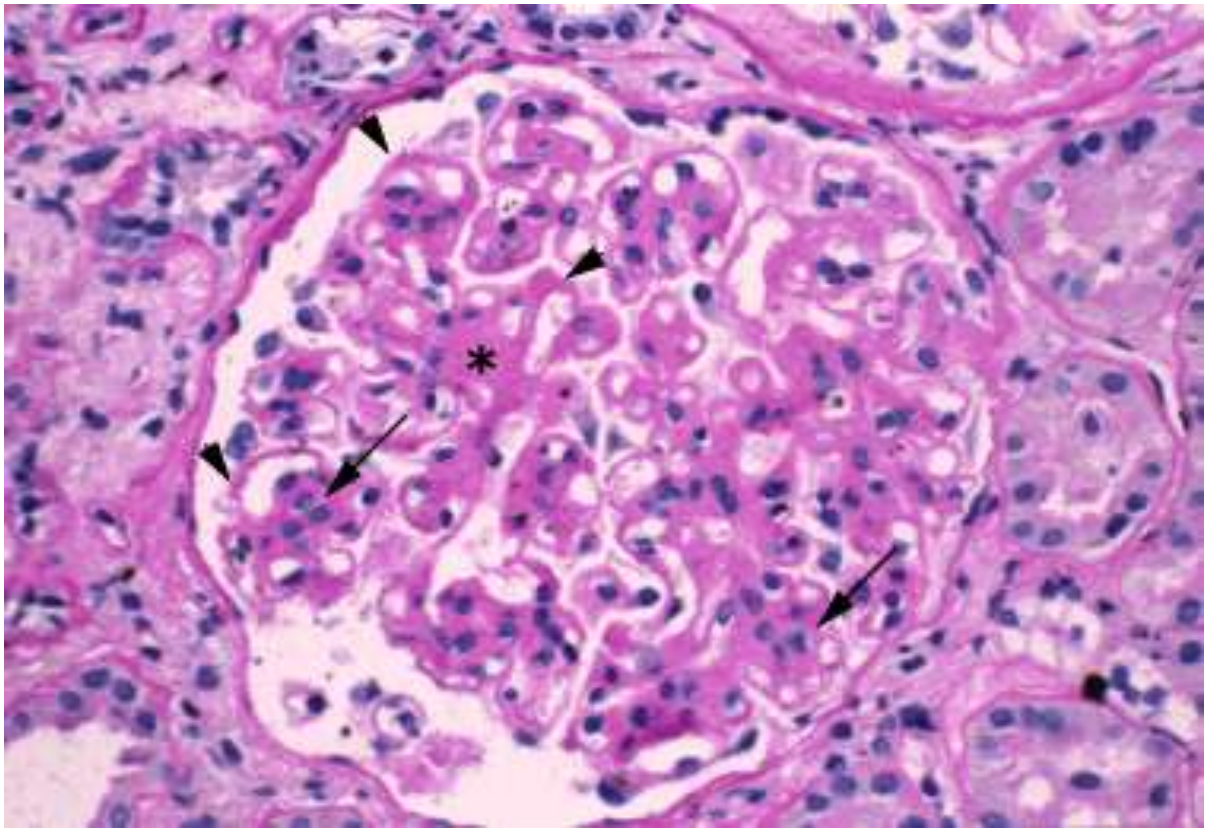
Paraproteinemias[a]
- Monoclonal gammopathy of undetermined significance
- Waldenstrom macroglobulemia
- Chronic lymphocytic leukemia
- Low-grade B-cell lymphoma
- Cyroglobulinemia types 1 and 2
- Immunotactoid glomerulopathy
- Monoclonal Ig deposition disease
- Fibrillary glomerulopathy



LIGHT MICROGRAPH OF A NORMAL GLOMERULUS. THERE ARE ONLY 1 OR 2 CELLS PER CAPILLARY TUFT, THE CAPILLARY LUMENS ARE OPEN, THE THICKNESS OF THE GLOMERULAR CAPILLARY WALL (LONG ARROW)



LM OF MPGN SHOWING THICKENING OF ALL CAPILLARY WALLS WITH DOUBLE CONTOURS (LONG ARROWS) AND FOCAL AREAS OF CELLULAR PROLIFERATION (SHORT ARROW).

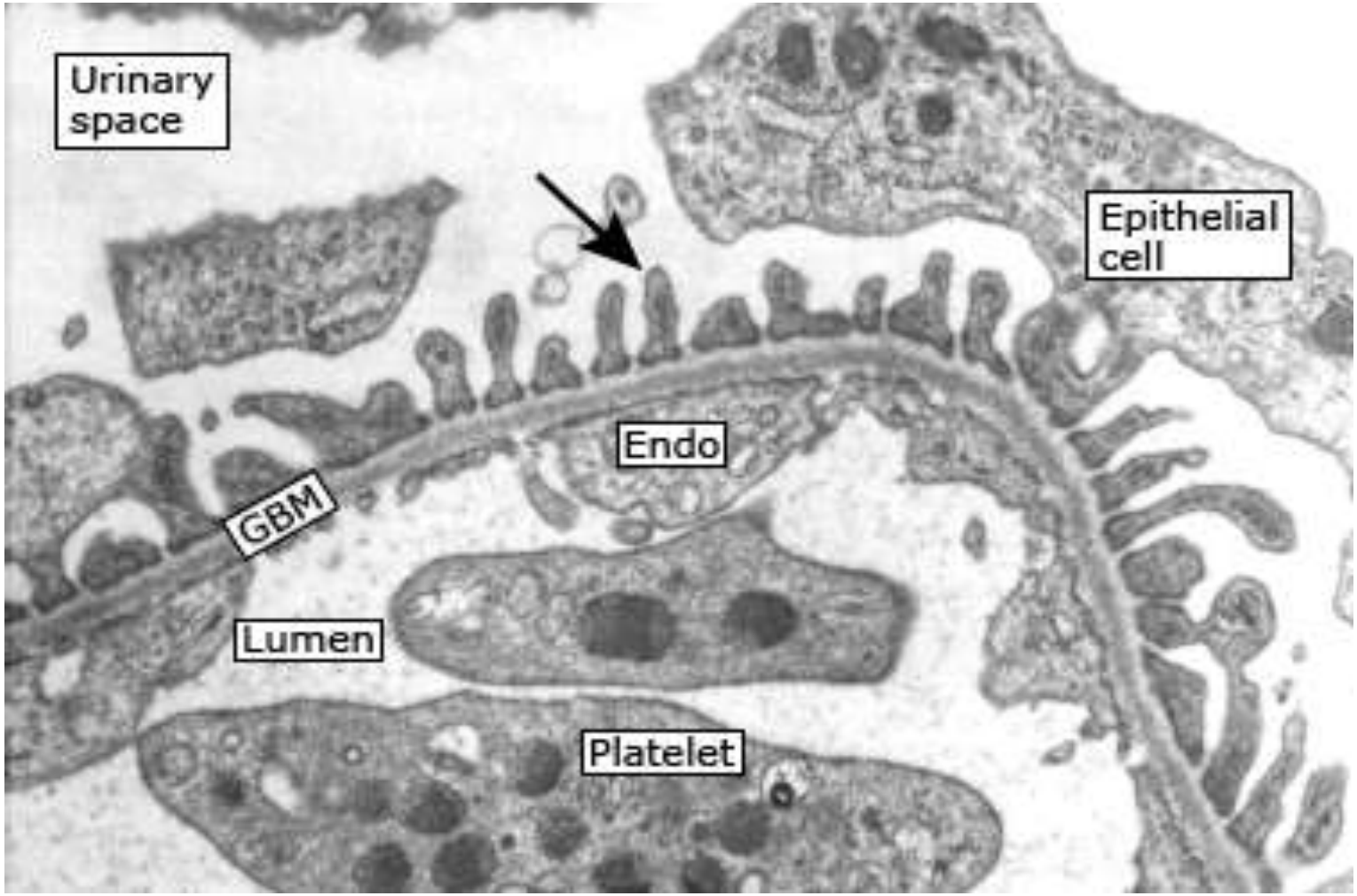


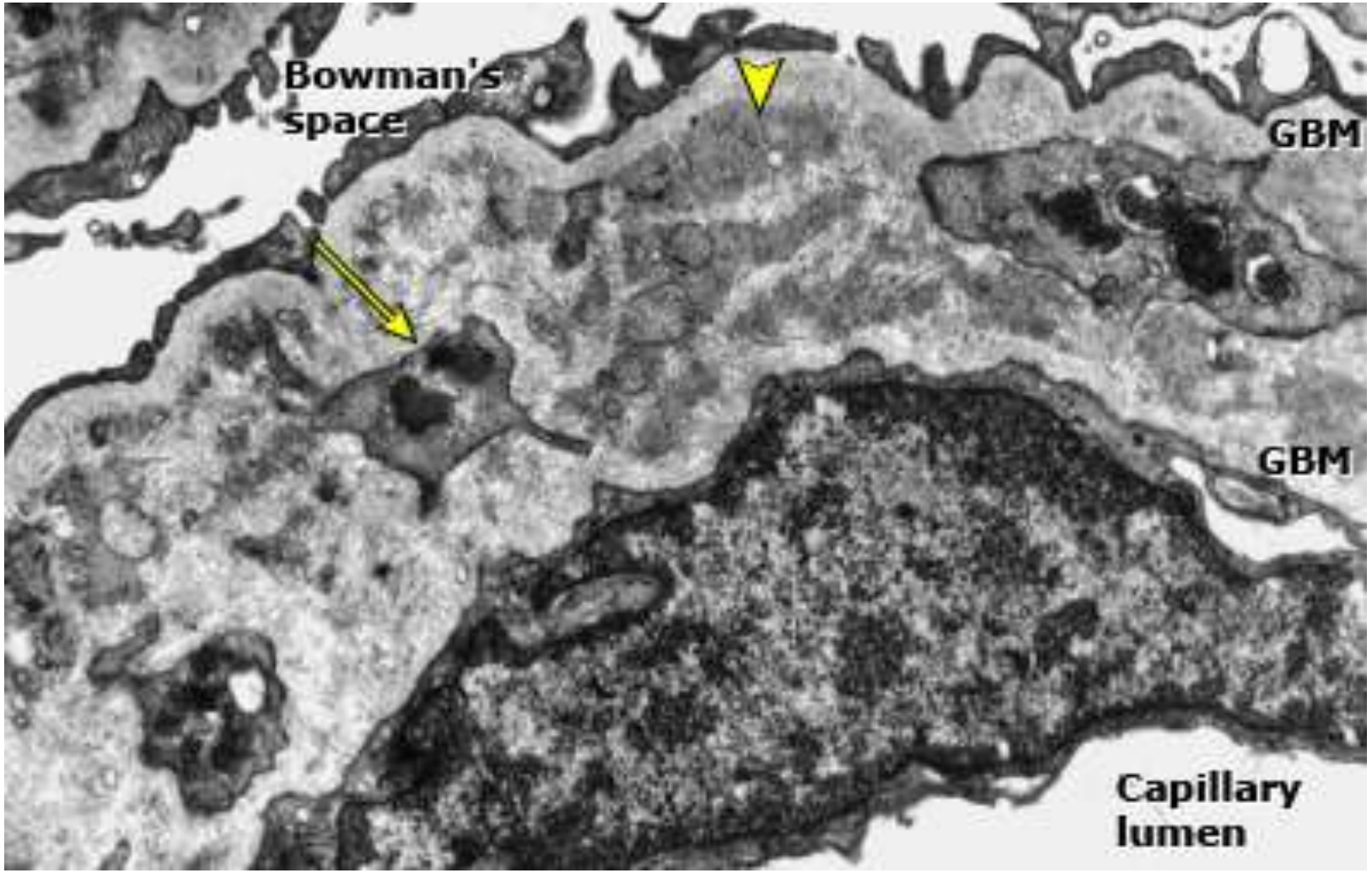
L M IN MPGN SHOWING A LOBULAR APPEARANCE OF THE GLOMERULAR TUFT WITH FOCAL AREAS OF INCREASED GLOMERULAR CELLULARITY (LARGE ARROWS), MESANGIAL EXPANSION (*), NARROWING OF THE CAPILLARY LUMENS, AND DIFFUSE THICKENING OF THE GLOMERULAR CAPILLARY WALLS (SMALL ARROWS).

CLASSIFICATION BASED UPON EM

- MPGN was initially classified into types I, II, and III based upon electron microscopy (EM).
- MPGN type I — MPGN type I is characterized by discrete immune deposits in the mesangium and subendothelial space, similar to that seen in lupus nephritis, that are thought to reflect the deposition of circulating immune complexes.

NORMAL GLOMERULUS

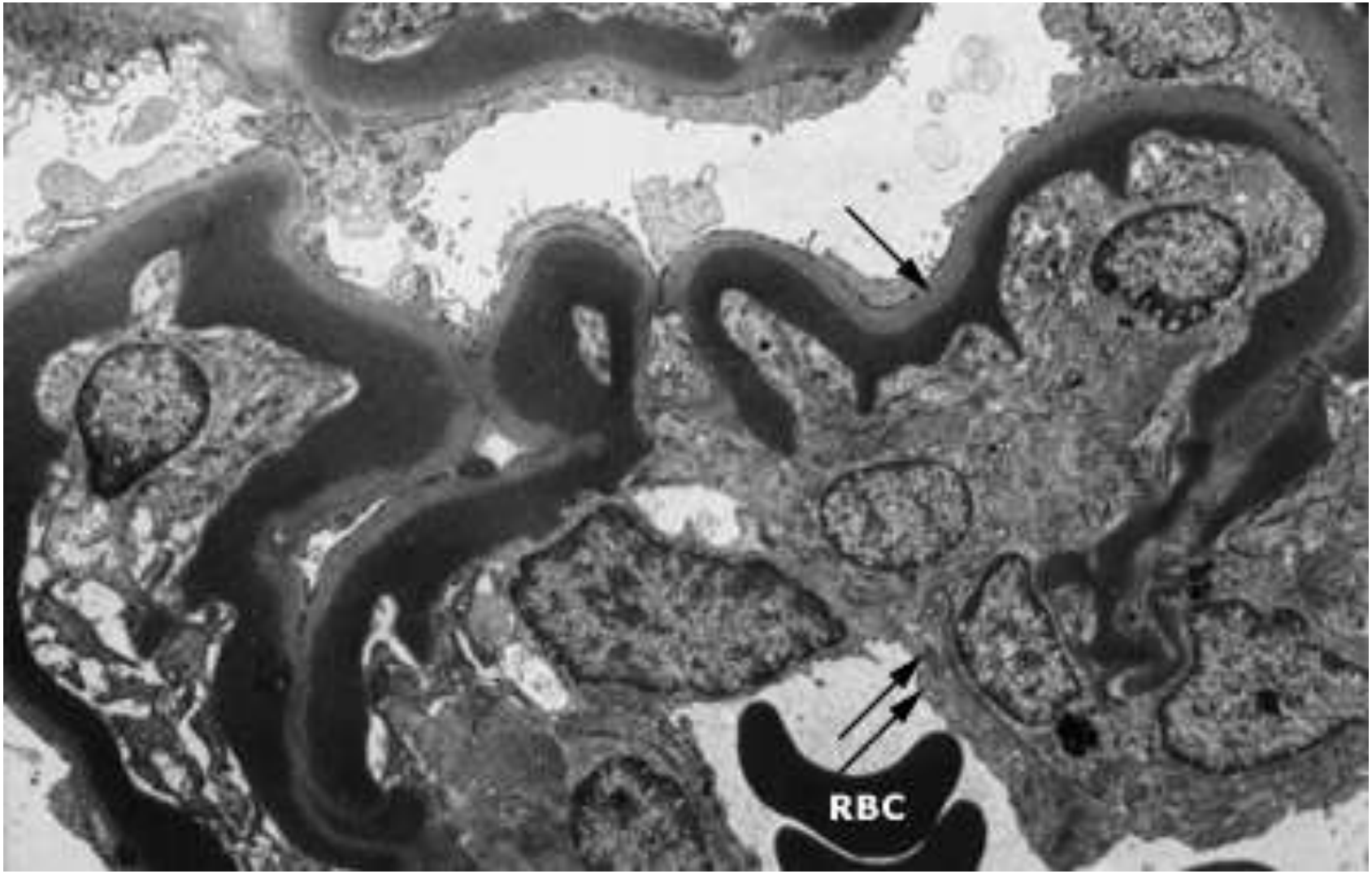




EM IN TYPE I MPGN SHOWS MARKED THICKENING OF THE GLOMERULAR CAPILLARY WALL BY IMMUNE DEPOSITS (ARROWHEAD) AND BY INTERPOSITION OF MESANGIAL CELL PROCESSES (ARROW). THERE ARE TWO LAYERS OF THE GLOMERULAR BASEMENT MEMBRANE (GBM) SURROUNDING THE MESANGIAL INTERPOSITION THAT ACCOUNT FOR THE DOUBLE-CONTOUR APPEARANCE ON LIGHT MICROSCOPY.

CLASSIFICATION BASED ON EM

- **MPGN type II — MPGN type II (dense deposit disease, or DDD) is characterized by continuous, dense ribbon-like deposits along the basement membranes of the glomeruli, tubules, and Bowman's capsule**



ELECTRON MICROGRAPH IN DENSE DEPOSIT DISEASE (DDD) SHOWING DENSE, RIBBON-LIKE APPEARANCE OF SUBENDOTHELIAL AND INTRAMEMBRANOUS MATERIAL (ARROW) AND NARROWING OF THE CAPILLARY LUMEN DUE TO PROLIFERATION OF CELLS (DOUBLE ARROW).

CLASSIFICATION BASED UPON EM

- **MPGN type III — MPGN type III is similar to MPGN type I except that subepithelial deposits are noted as well as subendothelial deposits**

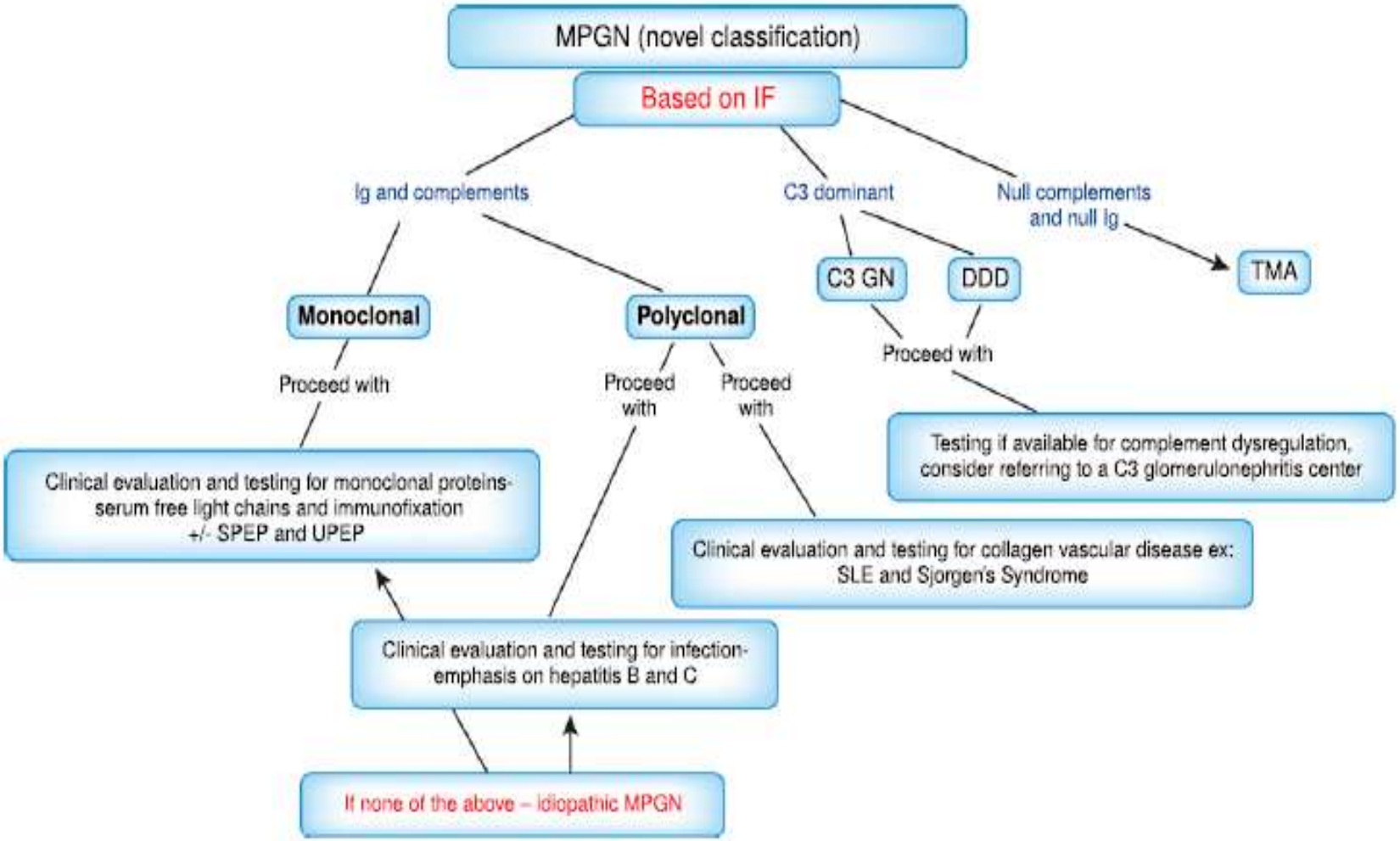
MPGN TYPE III. THIS ELECTRON MICROGRAPH SHOWS THE IRREGULAR APPEARANCE OF ELECTRON-DENSE, PRESUMED IMMUNE AGGREGATES WITHIN, OUTSIDE, AND UNDER THE GLOMERULAR CAPILLARY BASEMENT MEMBRANE.

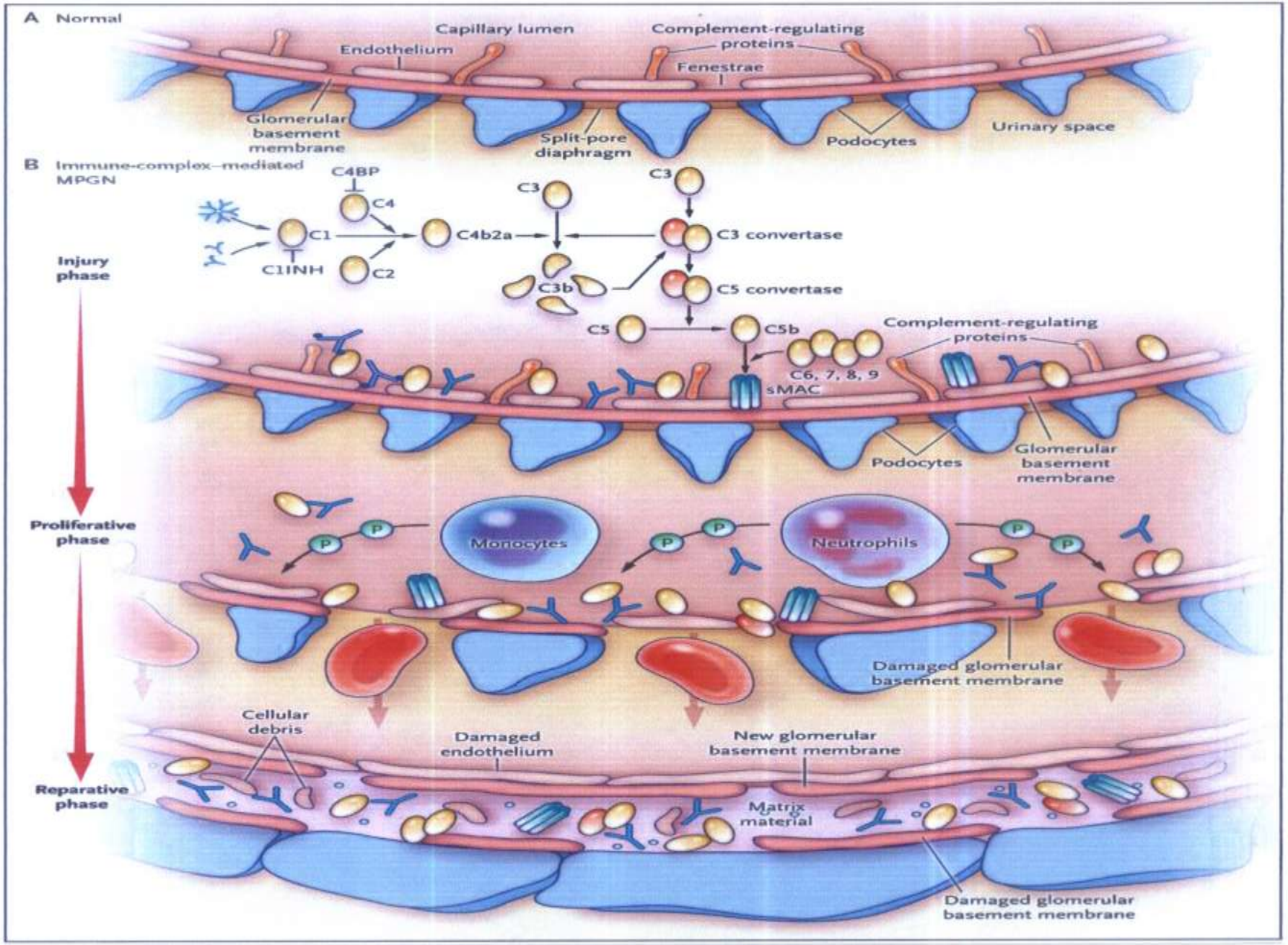
CLASSIFICATION BASED UPON EM

Limitations of this classification

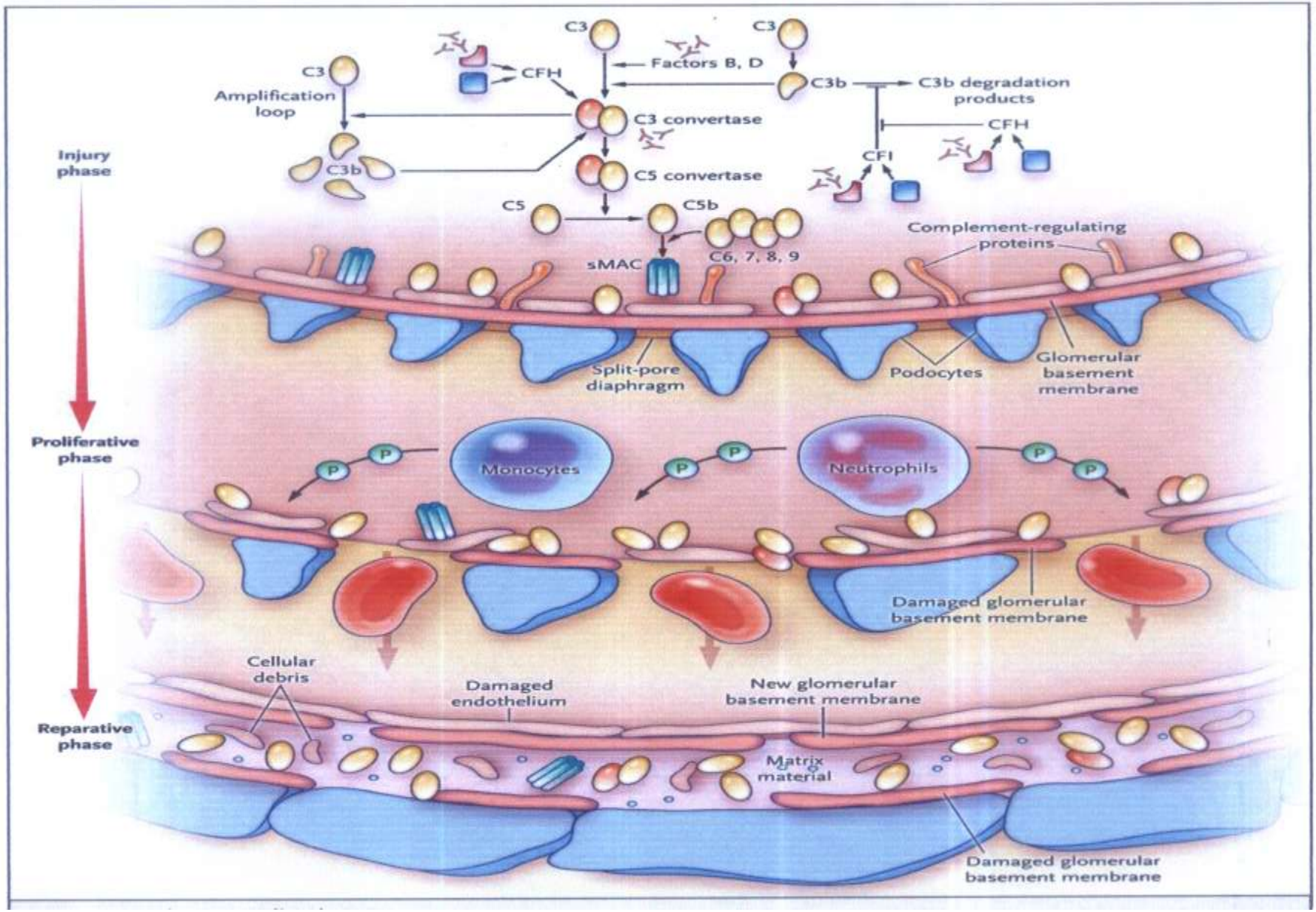
- **The EM-based classification can result in overlap between types I and III.**
- **Not based on pathogenesis – Multiple mechanisms of injury may result in a common pattern of injury.**
- **In contrast, a classification that is based upon the pathogenetic process helps to direct the clinical evaluation and to provide disease-specific treatments.**

IF CLASSIFICATION OF MPGN



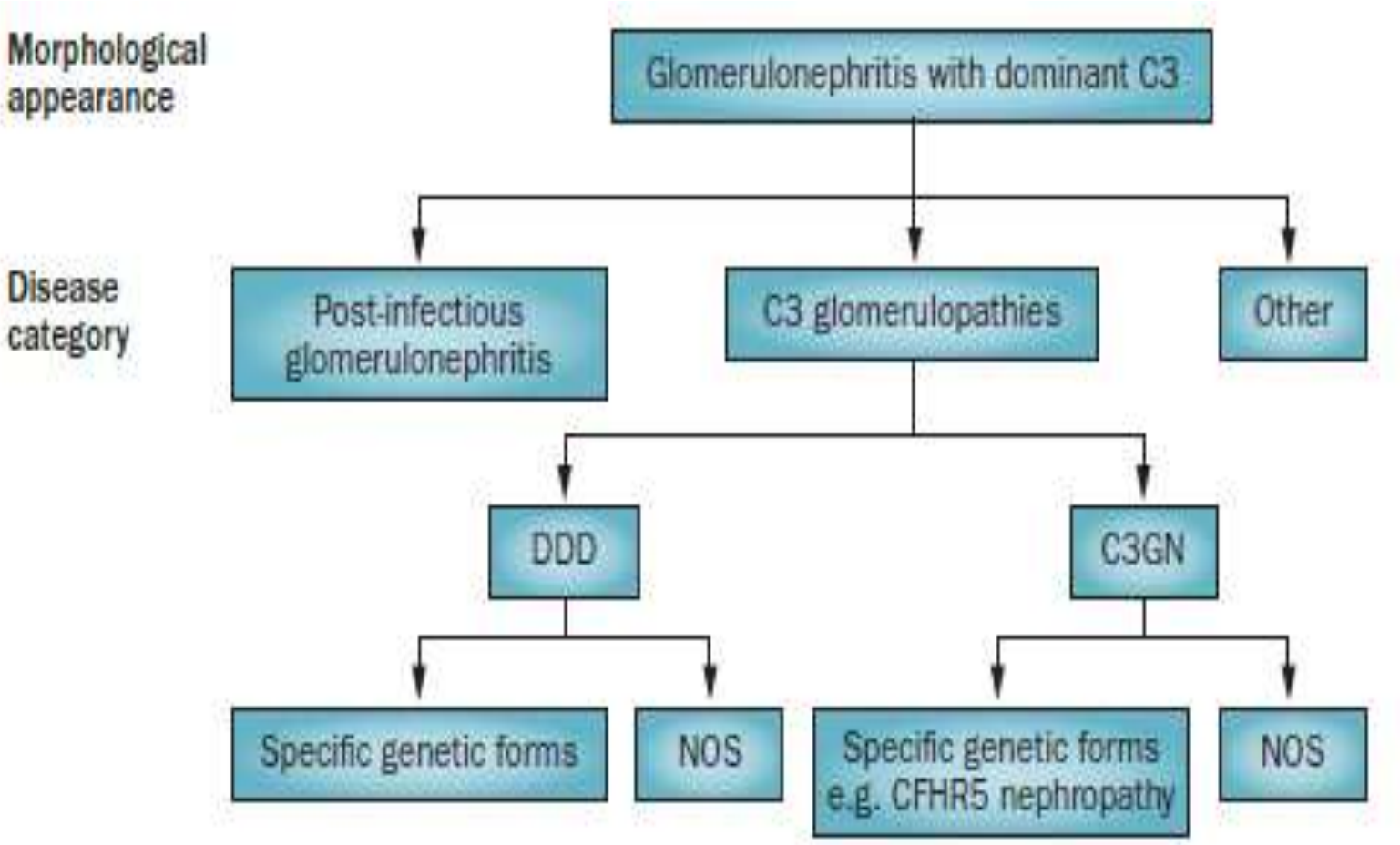


IC-Mediated MPGN



Complement-Mediated MPGN

C3 GLOMERUOLOPATHY



MPGN *TYPE* II

Dense Deposit Disease

- **Rare disease**
- **Mainly in children and young adults (5-15ys)**
- **Both genders equally**

- **Nephritic, Nephrotic Syndrome, Renal insufficiency**
- **Prognosis (50% ESRD within 10 ys)**

J Am Soc Nephrol 16: 1392-1403, 2005

MPGN *TYPE* II

Dense Deposit Disease

Pathogenesis

- Loss of complement regulation

C3 nephritic factor (IgG autoantibody)

- Mutations of factor H gene

J Am Soc Nephrol 16: 1392-1403, 2005

EPIDEMIOLOGY

DDD:

- **2 - 3 / million population**
- **Children and young adults.**
- **Male = Female**

O'Shaughnessy . *Clin J Am Soc Nephrol*. 2014;9:46-53.

CLINICAL MANIFESTATIONS

DDD:

A: Renal Manifestations:

100%: Proteinuria & hematuria.

2/3: Nephrotic-range proteinuria

12- 65%: frank nephrotic syndrome

Hypertension & RI: common

50% ESRD after 10 years.

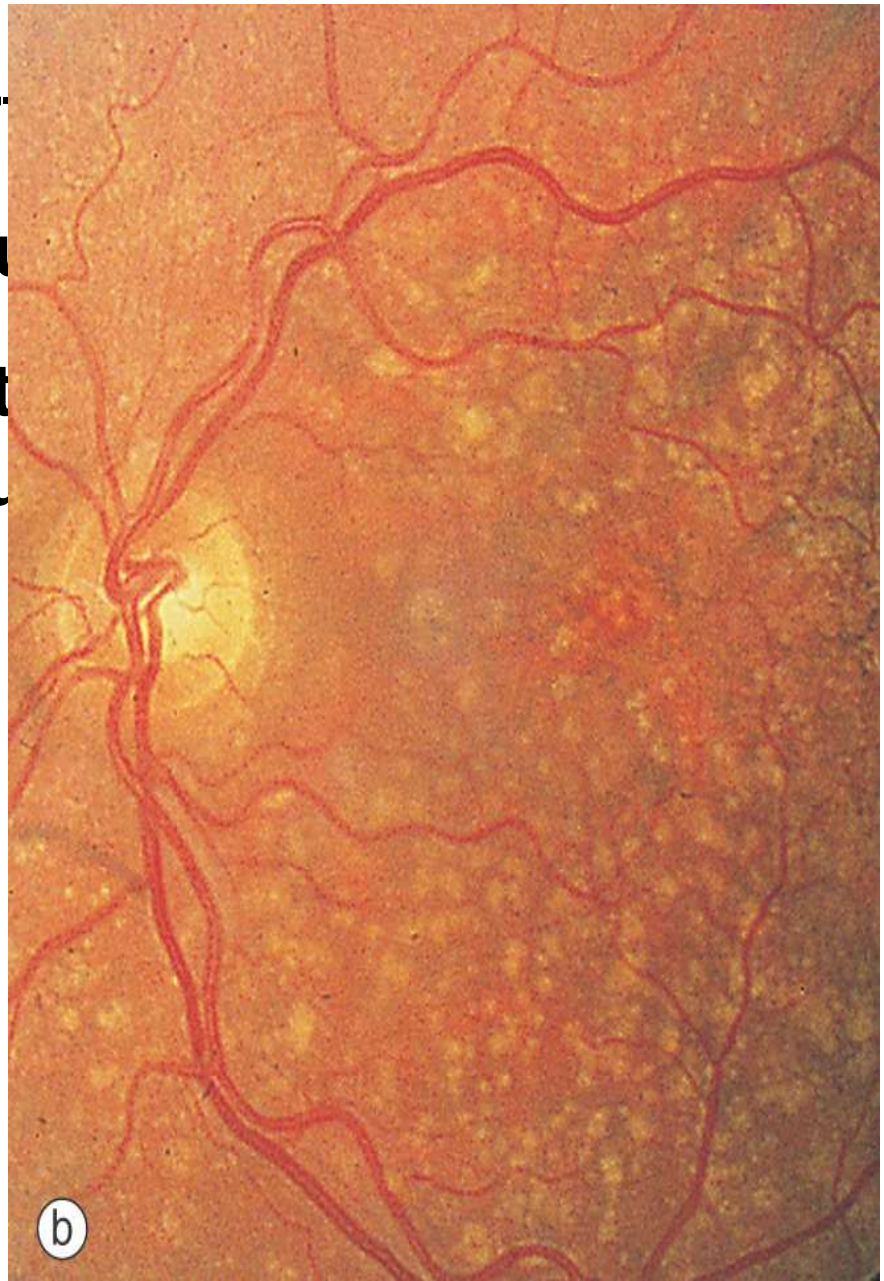
Nasr et al. *Clin J Am Soc Nephrol*. 2009;4:22-32.

B: Extrarenal Manifestations:

Par

Visu

Mot
(dru



C3 GLOMERULOPATHIES

- **Disease process caused by abnormal control of complement activation, deposition, or degradation.**
- **Alternative pathway.**
- **Characterized by predominant glomerular C3 fragment deposition with electron-dense deposits on EM.**

Servais et al. *Kidney Int*. 2012;82:454-464.

C3 GN

Recently recognized, clinical manifestations are less well defined.

French series:

- **27%; nephrotic syndrome at presentation**
- **2/3; microhematuria at presentation,**
- **1/3; elevated blood pressure.**

Servais A, et al. *Kidney Int*. 2012;82:454-464.

KNOWN MUTATION/CAUSES ASSOCIATED WITH C3GN

Autoantibodies to C3 convertase
Autoantibodies to factor H
Autoantibodies to factor B
Properdin deficiency
C3 nephretic factor
Complement factor H mutation screening identified the H402 allele and V62 allele
Heterozygous mutations in factor I gene
Heterozygous mutation in CD 46 gene (membrane cofactor protein)
Mutation in the gene for complement factor H-related protein 5

LABORATORY FINDINGS

C3:

- **Low; DDD (80%), C3GN (50 %).**
- **Normal: CFHR5 nephropathy.**

C1q and C4: normal.

C3NeF:

- **DDD: > 50% of patients.**
- **C3 GN: < 50% of patients.**
- **Non specific and not standardized.**

TREATMENT

Still undefined.

Eculizumab.

Several drugs for inhibition of C3 activation are in preclinical development.

Herlitz LC, et al. *J Am Soc Nephrol*. 2012;23:1229-1237.

TRANSPLANTATION & RECURRENCE

Primary:

- **MPGN: 20% - 30%.**
- **DDD: 50% - 100%.**

Secondary:

- **Directly linked to control of the underlying illness**

Choy BY et al. Am J Transplant 2006; 6:2535.

MPGN WITHOUT IMMUNOGLOBULIN OR COMPLEMENT DEPOSITION

A histologic pattern that may resemble MPGN on light microscopy can be seen in:

a) Healing phase of TMA (eg, TTP, HUS)

b) Antiphospholipid antibody syndrome,

c) Nephropathy with BM transplantation

d) Chronic renal allograft nephropathy

e) Radiation nephritis

f) Malignant hypertension.

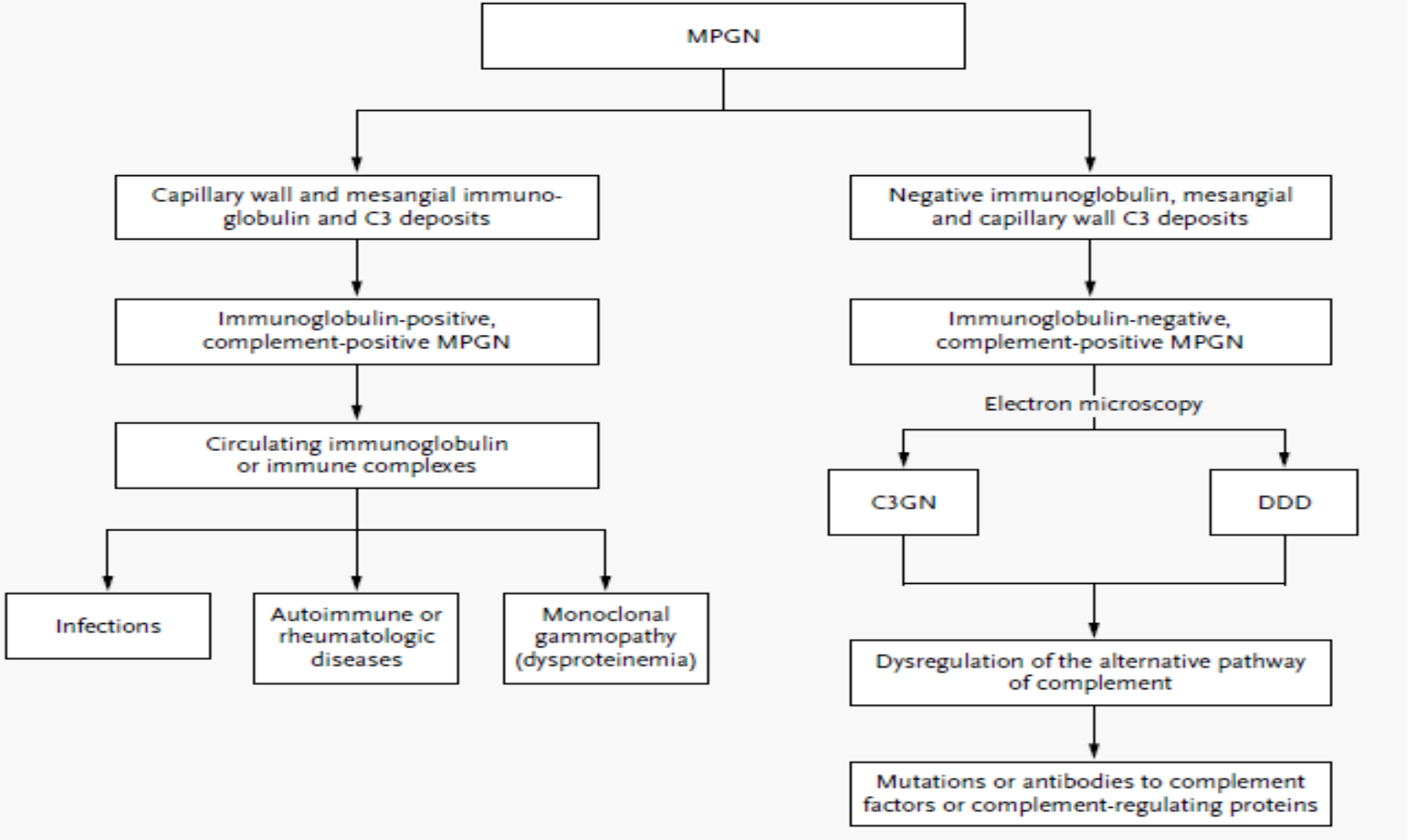
g) Scleroderma

KDIGO GUIDELINES FOR MANGMENT OF MPGN

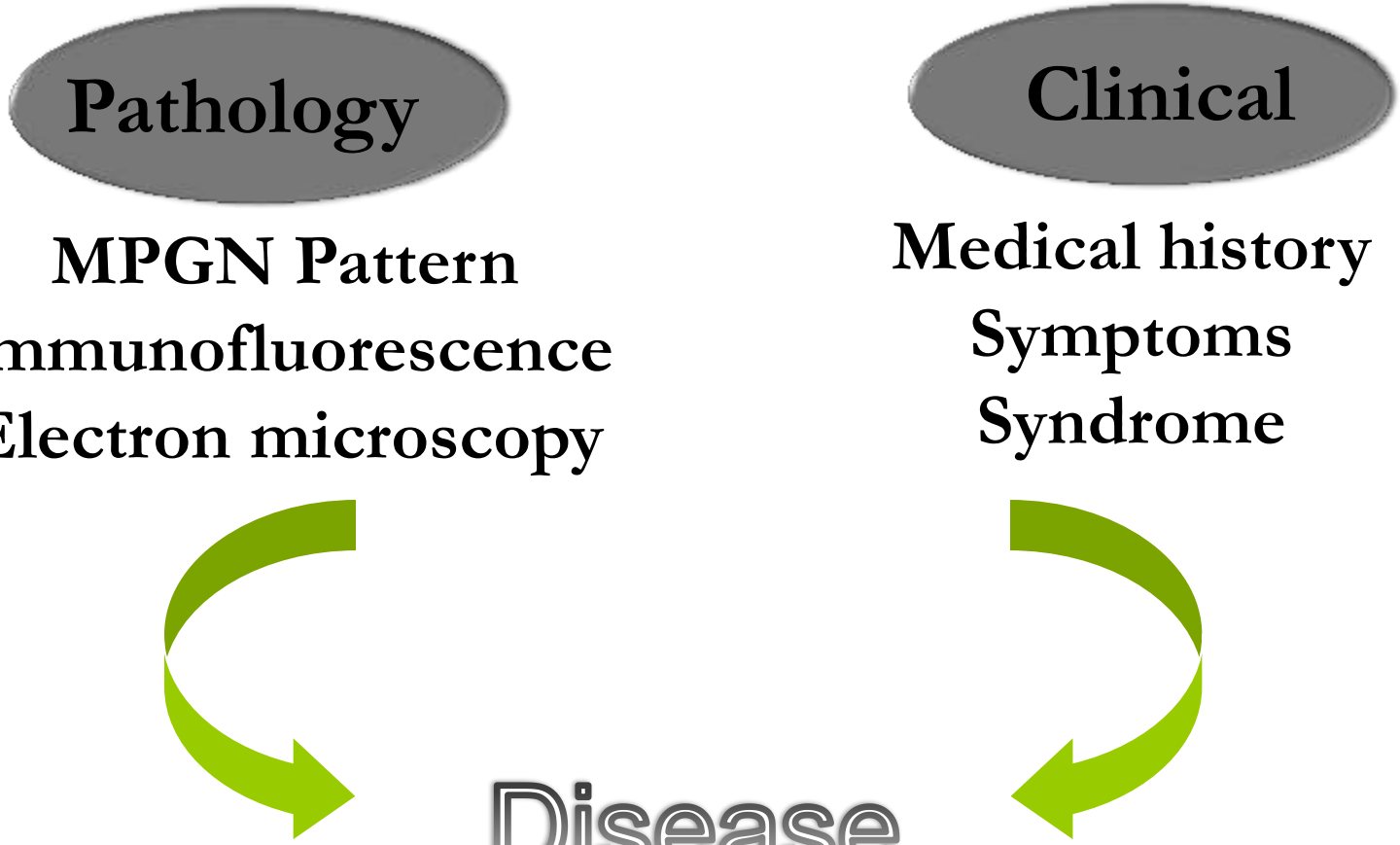
8.1.1: Evaluate patients with the histological (light-microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (see Table 20). (*Not Graded*)

8.2.1: We suggest that adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome *AND* progressive decline of kidney function receive oral cyclophosphamide or MMF plus low-dose alternate-day or daily corticosteroids with initial therapy limited to less than 6 months. (*2D*)

TAKE HOME MESSAGES



Take HOME Message



THANK YOU